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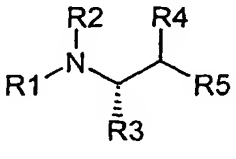
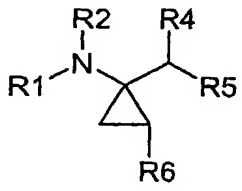
(54) Title: HCV NS-3 SERINE PROTEASE INHIBITORS



(I)



(II)

(57) Abstract: Compounds possessing novel P1 amino acid replacements of the formulae (I) or (II) where R^1 is a peptidic or peptidomimetic recognition sequence P2-Pn targeting the S2- Sn pockets of HCV NS-3 serine protease, where n is 3-6, which recognition sequence is peptide bonded to formula (I); R^2 is H, C_1-C_3 alkyl; R^3 is C_1-C_3 alkyl, optionally substituted with 1-3 halo atoms or -SH; R^4 is =O, halo, amino or -OH; R^5 is C_1-C_6 alkyl, C_0-C_3-alkylaryl, C_0-C_3-alkylhet, C_0-C_3-alkylcycloC$_3$-C$_6$-alkyl, any of which can be optionally substituted with hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkanoyl, amino, halo, carboxy, cyano, azido, mercapto, nitro, C_0-C_3-alkylaryl, C_0-C_3-alkylhet, C_0-C_3-alkylcycloalkyl; R^6 is H C_1-C_3 alkyl or cyclises with the nominal N-terminal to form a macrocycle; with the proviso that if R_4 is =O, then the alkyl moiety of R_5 as alkylaryl or alkylhet is C_1-C_3 alkanyl or C_2-C_3 alkenyl; have utility as HCV NS-3 serine protease inhibitors.

WO 2004/026896 A2

HCV NS-3 Serine Protease Inhibitors

Technical Field

This invention relates to inhibitors of the NS3 serine protease of the flavivirus HCV which have a novel P1 amino acid replacements and to methods for their use in the treatment or prophylaxis of HCV.

Background Art

The NS3 serine protease of HCV is a multifunctional protein which contains a serine protease domain and a RNA helicase domain. The protease cofactor NS4A, which is a relatively small protein, is absolutely required for enhanced serine protease activity. The NS3 serine protease is essential in the viral lifecycle. From analysis of the substrate binding site as revealed by X-ray crystal structure, it has been shown that the binding site of the NS3 protease is remarkably shallow and solvent exposed making small molecule inhibitor design a challenge. NS3 protease inhibitors in general fall into two structural classes characterised by either an electrophilic carbonyl P1 group, acting as classical serine-trap or warhead for the catalytic serine of the NS3 protease active site:

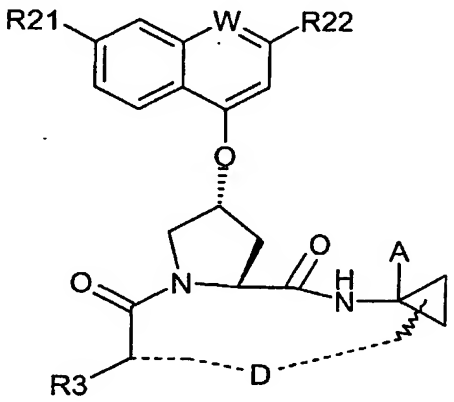
Steinkühler, 2001 Curr Med Chem 8 819-932
Narjes, 2002 Bioorg Med Chem Lett 12 701-704
Llinas-Brunet, 1998 Bioorg Med Chem Lett 8 2719-2724
Ede, 2000 J Pept Sci 6 11-18
Han, 2000 Bioorg Med Chem Lett 10 711-713
Colarusso, 2002 Bioorg Med Chem Lett 12 705-708
Zhang, 1998 Tet Lett 39 7439-7442
Bennett, 2001Bioorg Med Chem Lett 11355-357
Attwood, 1999 Antiviral Chem Chemother 10 259-273

or by having a P1 carboxylic acid characterised as product based inhibitors:

Steinkühler, 2001 Curr Med Chem 8 819-932
Llinas-Brunet, 1998 Bioorg Med Chem Lett 8 2719-2724
Poupart, 2001 J Org Chem 66 4743-4751
Steinkühler, 1998 Biochem 37 8899-8905

Ingallinella, 1998 Biochem 37 8906-8914
Llinas-Brunet, 2000 Biorg Med Chem Lett 10 2267-2270
Narjes, 2002 Bioorg Chem Med Lett 12 701-4].

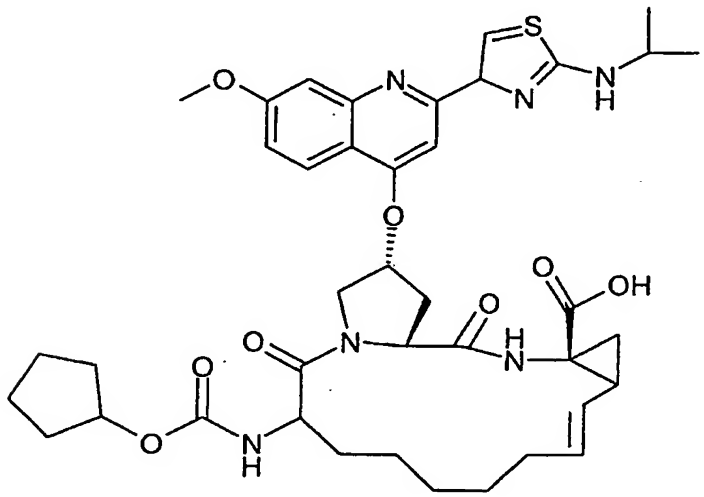
In the patent literature, Boehringer Ingelheim's WO 00/09543 & WO 00/09558 disclose peptidomimetics bearing a 1-aminocyclopropane-1-carboxylic acid P1. WO 00/59929 discloses similar P1 groups wherein the N-terminus of the peptidomimetic is cyclised onto the cyclopropyl group to define a macrocycle of the generic formula (employing the variable names defined therein, rather than those of the present claims):



wherein

W is CH or N; R21 is H, halo, C1-6 alkyl, C3-6 cycloalkyl, C1-6 haloalkyl, C1-6 alkoxy, C3-C6 cycloalkoxy, hydroxy, or $N(R23)_2$, wherein each R23 is independently H, C1-6 alkyl or C3-C6 cycloalkoxy; and R22 is H, halo, C1-6 alkyl, C3-6 cycloalkyl, C1-6 haloalkyl, C1-6 thioalkyl, C1-6 alkoxy, C3-6 cycloalkoxy, C2-7 alkoxyalkyl, C3-6 cycloalkyl, C6 or 10 aryl or Het, wherein Het is a five-, six-, or seven-membered saturated or unsaturated heterocycle containing from one to four heteroatoms selected from nitrogen, oxygen and sulfur; said cycloalkyl, aryl or Het being substituted with R24, wherein R24 is H, C1-6 alkyl, C3-6 cycloalkyl, C1-6 alkoxy, C3-6 cycloalkoxy, NO_2, $N(R25)_2$, NH-C(O)-R25; or NH-C(O)-NH-R25, wherein each R25 is independently: H, C1-6 alkyl or C3-6 cycloalkyl; or R24 is NH-C(O)-OR26 wherein R26 is C1-6 alkyl or C3-6 cycloalkyl; R3 is hydroxy, NH_2, or a group of formula -NH-R31, wherein R31 is C6 or 10 aryl, heteroaryl, -C(O)-R32, -C(O)-OR32 or -C(O)-NHR32, wherein R32 is: C1-6 alkyl or C3-6 cycloalkyl; D is a 5 to 10-atom saturated or unsaturated alkylene chain optionally containing one to three heteroatoms independently selected from: O, S, or N-R41, wherein R41 is H, C1-6 alkyl, C3-6 cycloalkyl or -C(O)-R42, wherein R42 is C1-6 alkyl, cycloalkyl or C6 or

10 aryl; R4 is H or from one to three substituents at any carbon atom of said chain D, said substituent independently selected from the group consisting of: C1-6 alkyl, C1-6 haloalkyl, C1-6 alkoxy, hydroxy, halo, amino, oxo, thio or C1-6 thioalkyl, and A is an amide of formula -C(O)-NH-R5, wherein R5 is selected from the group consisting of: C1-8 alkyl, C3-6 cycloalkyl, C6 or 10 aryl or C7-16 aralkyl; or A is a carboxylic acid; such as their phase II drug BILN2061:



Each of the applications in the immediately preceding paragraph together with WO 99/07734 & WO 99/07733 disclose substituted proline P2 groups.

Bristol Myers Squibb/DuPont's WO 02/60926 also discloses a 1-aminocyclopropane-1-carboxylic acid P1 and substituted proline P2. WO 02/48157, WO 02/48116 & WO 01/64678 disclose proline peptidomimetics in conjunction with a boron trap. WO 01/64678 discloses a boron serine trap, together with an alkyl or alkenyl P1 and a fused proline P2. WO 01/40262 disclose an alpha ketoamide warhead, inter alia with alkyl at P1 and aliphatic amino acids at P2, P3 and P4. WO 01/07407 discloses lactams in conjunction with the boron serine trap, while WO 01/02424 discloses the boron trap in conjunction with alkyl or alkylene at P1 and proline at P2.

Eli Lilly's WO 02/18369 discloses a fused proline P2, alkyl or alkenyl P1 and diketo or difluoro warhead.

Schering's WO 02/48172 and WO 02/08244 disclose spiro-proline P2 groups in conjunction with alkyl or alkenyl P1 and a diketo warhead. WO 02/08265 discloses the diketo warhead, similar P1, but a conventional proline P2, whereas WO 02/08198 discloses a diaza-proline

replacement bearing a ketone function and an N-benzyl substituent with the alkyl/alkenyl P1 and diketo warhead. WO 02/08187 describes peptoids with various P2, P3 and P4 functionalities. WO 01/81325 and WO 01/77113 disclose a diketo warhead, alkyl/alkenyl P1 and a macrocyclic ring system incorporating P2 and P3 functionalities. WO 01/58929 discloses a diaza peptidomimetic at P1 in conjunction with proline P2.

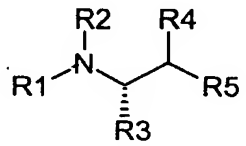
Vertex' WO 99/50230 discloses phenyl or naphthyl replacements for proline at P2. WO 01/74768 discloses ester substituted proline at P2, alkyl at P1 with a diketo warhead.

Each of the patent applications above tend to employ aliphatic amino acids at P3 and P4 (where present) with a variety of conventional pharmaceutically acceptable capping groups, typically aryloyl or heteroaryloyl at the N-terminus.

Clearly the above patent disclosures provide ample guidance in the choice and synthesis of appropriate amino acid or peptidomimetic of P2, P3, and if present, P4, P5 or P6 residues for coupling with the novel P1 amino acid replacements described herein. Accordingly the disclosure of each of these patents is specifically incorporated herein for these purposes.

Brief Description of the Invention.

In accordance with a first aspect of the invention, there is provided a compound of the formula I:



I

where

R^1 is a peptidic or peptidomimetic recognition sequence P2-Pn targeting the S2- Sn pockets of HCV NS-3 serine protease, where n is 3-6, which recognition sequence is peptide bonded to formula I

R^2 is H, C_1-C_3 alkyl;

R^3 is C_1-C_3 alkyl, optionally substituted with 1-3 halo atoms or –SH.

R^4 is =O, –OH, amine or halo.

R^5 is C_1-C_6 alkyl, C_0-C_3-alkylaryl, C_0-C_3alkylhet, C_0-C_3alkylcycloC_3-C_6alkyl, any of which can be optionally substituted with hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 alkoxy

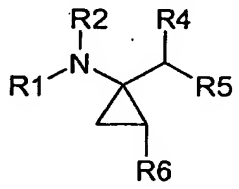
C_1-C_6 alkyl, C_1-C_6 alkanoyl, amino, halo, carboxy, cyano, azido, mercapto, nitro, C_0-C_3-alkylaryl, C_0-C_3alkylhet, C_0-C_3alkylcycloalkyl;

with the proviso that if R_4 is =O, then the alkyl moiety of R_5 as alkylaryl or alkylhet is C_1-C_3 alkanyl or C_2-C_3 alkenyl

and pharmaceutically acceptable salts thereof.

Preferably, R^3 is n-ethyl, n-propyl, 2,2-difluoroethyl or mercaptomethyl.

A second aspect of the invention provides a compound of the formula II:



II

where

R^1 is a peptidic or peptidomimetic recognition sequence targeting the S2- Sn pockets of HCV NS-3 serine protease, where n is 3-6, which recognition sequence is peptide bonded to formula II;

R^2 is H, C_1-C_3 alkyl;

R^4 is =O, –OH, halo or amino

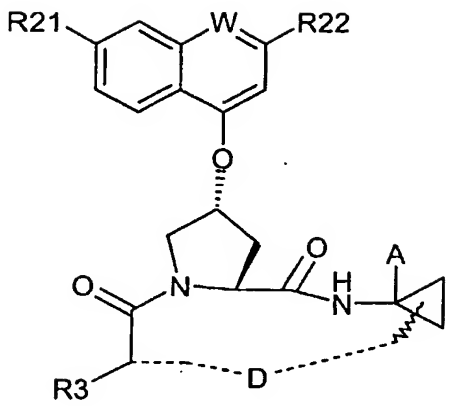
R^5 is C_1-C_8 alkyl, C_0-C_3-alkylaryl, C_0-C_3alkylhet, C_0-C_3alkylcycloalkyl, any of which can be optionally substituted with hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkanoyl, amino, halo, carboxy, cyano, azido, mercapto, nitro, C_0-C_3-alkylaryl, C_0-C_3alkylhet, C_0-C_3alkylcycloalkyl;

R^6 is H or C_1-C_3 alkyl;

with the proviso that if R_4 is =O, then the alkyl moiety of R_5 as alkylaryl or alkylhet is C_1-C_3 alkanyl or C_2-C_3 alkenyl

and pharmaceutically acceptable salts thereof.

Preferably, R^6 is H or -$CHCH_2$. Alternatively, R6 can cyclise with the (nominal) N-terminal of the compound to define a macrocycle, as shown in WO00 59929 discussed above, ie



wherein the variables are as defined above (including each of the preferments and embodiments of WO 00/59929, but wherein A represents the -C(R_4)R_5; moiety of the present Formula II.

Conveniently R^5 is straight or branched C_3-C_8 alkyl, optionally containing a single unsaturated bond. Preferably, the alkyl moiety of R^5 is C_1 – C_3 alkanyl or C_2-C_3 alkenyl.

Other preferred R^5 groups include C_0-C_3-alkylaryl, such as optionally substituted phenyl or benzyl, or C_0-C_3-alkylhet, such as optionally substituted, pyridyl, pyridylmethyl, thiazolyl, thiozolylmethyl, piperazinyl, morpholinyl and piperidinyl.

Preferably R^2 is H.

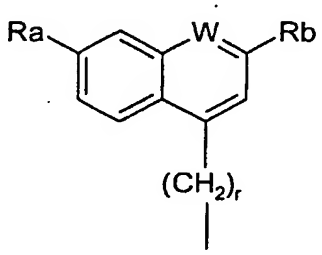
Conveniently R^4 in formula I or II is =O. Unexpectedly however, we have found that R^4 are halo, amino and especially hydroxy - provide reversible inhibitors of considerable potency. Accordingly, preferred R^4 groups include chloro and especially fluoro, amino, especially -NH_2 and hydroxy.

R^1 as a peptidic sequence comprises 2-5 peptide bonded, natural or non-natural amino acids, preferably 2 or 3 residues, which sequence is stereochemically adapted to fit the S2-Sn subsite of HCV NS-3, (the peptide sequence being conventionally designated as P2, P3 etc with increasing numbers towards the N terminus of the compound) the structure of which subsite is published and well known. A large number of examples are illustrated in the academic and especially the patent literature discussed above. The N amino terminus of the sequence is typically capped with a conventional pharmaceutically acceptable capping group, or cyclised with R6 or the P2 side chain as defined above. One or more of the peptide bonds in such a sequence may be replaced

with a conventional peptide isostere such as –N-N- to form a peptidomimetic which will typically leave the essential spatial relationship of the various amino acid side chains substantially unchanged.

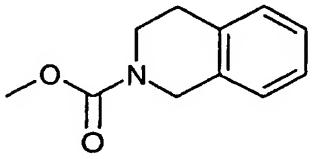
Preferably P2 of R^1 is the amino acid proline or 4-hydroxyproline, which hydroxy function is optionally etherified or esterified to a C_0-C_3 aryl or C_0-C_3het group, either of which may be optionally substituted. Suitable ether or ester substituents are disclosed in WO 00/59929, WO 00/09543, WO 00/09558, WO 99/07734, WO 99/07733, WO 02/60926.

A preferred ether substituent has the formula



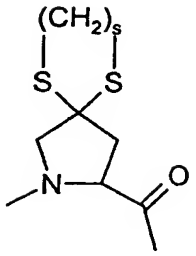
where W is N or CH, r is o or 1, Ra is H, C_1-C_6 alkyl, C_0-C_3cycloalkyl, C_1-C_6 alkyloxy, hydroxy or amine and Rb is H, halo, C_1-C_6 alkyl, C_0-C_3cycloalkyl, C_1-C_6 alkyloxy, C_1-C_6 thioalkyl, cycloalkylC_0-C_3alkyloxy, C_1-C_3alkyloxyC_1-C_3alkyl, C_0-C_3aryl or C_0-C_3het. A particularly preferred ether substituent is 7-methoxy-2-phenyl-quinolin-4-yl oxy.

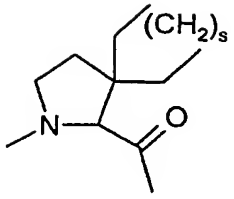
Preferred P2 proline ester substituents include those disclosed in WO 01/74768 such as C_1-C_6 alkyl, C_0-C_3aryloyl, particularly (optionally substituted) benzoyl or C_0-C_3 het-oyl, especially



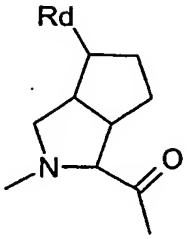
Alternative P2 proline substituents, as shown in WO 01/74768 include C_1-C_6 alkyl, such as ethyl, isopropyl, C_0-C_3-cycloalkyl such as cyclohexyl, 2,2-difluoroethyl, -C(=O)NRc, where Rc is C_1-C_6 alkyl, C_0-C_3-cyclopropyl, C_0-C_3-aryl or C_0-C_3-het.

A further form of substituted proline for P2 are the spiro –S-alkyl-S- compounds disclosed in WO 02/48172 and WO 02/08244:





where s is 2 or 3 or the fused rings:

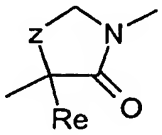


where Rd is H or =O, as shown in WO 01/74768 and WO 02/18369.

A still further form of substituted proline are the ethers shown in WO 01/77113, where the N terminus capping group cyclises with 4-hydroxyproline function to define a macrocycle.

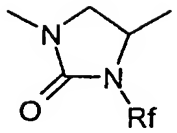
Proline P2 peptidomimetics include imidazolidinones as shown in WO 02/48157 or fused pyrimidinones as shown in WO 02/48116 or fused pyrazinones or triazinones as shown in WO 01/64678.

Further P2 proline peptidomimetics include the lactams shown in WO 01/07407:



where z is methyylene or ethylene and Re is Et, Pr, I-Pr, s-Bu, C_0-C_3aryl.

Still further P2 proline peptidomimetics include those shown in WO 02/08198:



where Rf is C_1-C6 alkyl, C_0-C_3-alkylaryl, C_0-C_3alkylhet, C_0-C_3alkylcycloalkyl, C_1-C_3alkyl(=O)O-C_1-C_3alkyl, especially benzyl.

Preferred P3 groups include aliphatic amino acid s, such as L-valyl, L-leucyl, L- isoleucyl or L-t-leucyl. Further preferred P3 groups, as shown in WO 02/01898 include C_0-C_3 cycloalkyl, especially cyclohexylalanine, optionally substituted with CO_2Rg, where Rg is H, is C_1-C6 alkyl, C_0-C_3-alkylaryl, C_0-C_3alkylhet, C_0-C_3alkylcycloalkyl or amine; or N-acetylpiperidine or tetrahydropyran.

Preferred P4 groups, if present, include aliphatic amino acid such as L-valyl, L-leucyl, L-isoleucyl , L-t-leucyl or L-cyclohexylalanine.

Preferred P5 groups, if present, include the amino acids D-Glu, gamma-carboxy-D-Glu or D-Val.

Preferred P6 groups, if present, include the amino acid L- Asp.

Conveniently, the amine function in the terminal amino acid (whether P3, P4, P5 or P6) is capped with a conventional pharmaceutically acceptable capping group.

The properties of many conventional N-protecting groups, as illustrated in Greene, Protecting Groups In Organic Chemistry, John Wiley, NY, are appropriate for capping groups..

Convenient pharmaceutically acceptable protecting groups have the formula -*C(=O)*R^{10} or -O-C(=O)-R^{10}, where R^{10} is C_0-C_3 aryl, C_1-C_6 alkyl, C_0-C_3-cycloalkyl, or C_0-C_3 het, any of which may be optionally substituted with halo, hydroxy, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy-C_1-C_6 alkyl, C_1-C_6 alkanoyl, amino, azido, oxo, mercapto, nitro, C_0-C_3aryl, C_0-C_3-cyclopropyl or C_0-C_3het.

Preferred capping groups include t-butyloxycarbonyl, benzoyl, benzoyloxy, pyridoyl, pyridoyloxy, furoyl, furoyloxy, thienoyl, thienoyloxy pyrimidoyl, or pyrimidoyloxy, any of

which is optionally substituted with one to three substituents selected from halo, hydroxy, nitro, cyano, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy-C_1-C_6 alkyl, C_1-C_6 alkanoyl, amino, azido, oxo, mercapto and nitro.

Particularly preferred capping groups include acetyl, t-butyloxycarbonyl, benzyloxycarbonyl, pyridylcarbonyl or pyrimidylcarbonyl.

Unnatural amino acids include L-amino acids wherein the side chain is not one of the 20 naturally occurring amino acids. Examples of non-natural amino acids include L-beta-methylsulfonylmethylalanine, L-cyclohexylalanine, L-tertiary-leucine, L-norleucine, L-norvaline, L-ornithine, L-sarcosine, L-citurline, L-homophenylalanine, L-homoserine, L-beta-(1-napthyl)alanine, L-beta-(2-napthyl)alanine etc. Non natural amino acids also include the D-amino acids corresponding to the 20 natural amino acids and D-amino acids bearing other side chains, such as those listed above.

'C_1-C_6-alkyl' as applied herein is meant to include straight and branched chain aliphatic carbon chains such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, pentyl, isopentyl, hexyl, heptyl and any simple isomers thereof. The alkyl group may have an unsaturated bond. Additionally, any C_1-C_6-alkyl may optionally be substituted by one or two halogens and/or a heteroatom S, O, NH. If the heteroatom is located at a chain terminus then it is appropriately substituted with one or 2 hydrogen atoms.

'C_1-C_3-alkyl' as applied herein includes methyl, ethyl, propyl, isopropyl, cyclopropyl, any of which may be optionally substituted as described in the paragraph above or in the case of C_2 or C_3, bear an unsaturated bond such as CH_2=CH.

'Amine' includes NH_2, NHC_1.C_3-alkyl or $N(C_1$-C_3-alkyl$)_2$.

'Halo' as applied herein is meant to include F, Cl, Br, I, particularly chloro and preferably fluoro.

'C_0-C_3-cycloalkyl' or 'C_0-C_3-cycloC_3-C_6alkyl' as applied herein is meant to include a C3-6 saturated or unsaturated carbocyclic ring such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cyclohexenyl, which is bonded directly (ie C_0) or through an intermediate methyl, ethyl, propyl, or isopropyl group.

'C_0-C_3-aryl' as applied herein is meant to include a phenyl or naphthyl which is directly bonded (ie C_0) or through an intermediate methyl, ethyl, propyl, or isopropyl group. Optionally the aryl group is substituted with 1-3 substituents selected from halo, hydroxy, nitro, cyano, carboxy, C_1-

C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy-C_1-C_6 alkyl, C_1-C_6 alkanoyl, amino, azido, oxo, mercapto, nitro C_0-C_3aryl, C_0-C_3-cyclopropyl or C_0-C_3het.

'C_0-C_3-het' as applied herein is meant to include a monocyclic heteroatom-containing ring such as piperidinyl, morpholinyl, piperazinyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazinolyl, isothiazinolyl, thiazolyl, oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, furanyl, thienyl, pyridyl, pyrimidyl, pyridazinyl, pyrazolyl, or any of such groups fused to a phenyl ring, such as quinolinyl, benzimidazolyl etc, which hetero ring is bonded directly e ie (C_0) or through an intermediate methyl, ethyl, propyl, or isopropyl group. Optionally the hetero ring is substituted with 1-3 substituents selected from halo, hydroxy, nitro, cyano, carboxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy-C_1-C_6 alkyl, C_1-C_6 alkanoyl, amino, azido, oxo, mercapto, nitro, C_0-C_3aryl, C_0-C_3-cyclopropyl or C_0-C_3het.

If a chiral centre is present, all isomeric forms are intended to be covered.

While it is possible for the active agent to be administered alone, it is preferable to present it as part of a pharmaceutical formulation. Such a formulation will comprise the above defined active agent together with one or more acceptable carriers or excipients and optionally other therapeutic ingredients. The carrier(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient.

The formulations include those suitable for rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration, but preferably the formulation is an orally administered formulation. The formulations may conveniently be presented in unit dosage form, e.g. tablets and sustained release capsules, and may be prepared by any methods well known in the art of pharmacy.

Such methods include the step of bringing into association the above defined active agent with the carrier. In general, the formulations are prepared by uniformly and intimately bringing into association the active agent with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product. The invention extends to methods for preparing a pharmaceutical composition comprising bringing a compound of Formula I or its pharmaceutically acceptable salt in conjunction or association with a pharmaceutically acceptable carrier or vehicle. If the manufacture of pharmaceutical formulations involves intimate mixing of pharmaceutical excipients and the active ingredient in salt form, then it is often preferred to use excipients which are non-basic in nature, i.e. either acidic or neutral.

Formulations for oral administration in the present invention may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active agent; as a powder or granules; as a solution or a suspension of the active agent in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water in oil liquid emulsion and as a bolus etc.

With regard to compositions for oral administration (e.g. tablets and capsules), the term suitable carrier includes vehicles such as common excipients e.g. binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, polyvinylpyrrolidone (Povidone), methylcellulose, ethylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, sucrose and starch; fillers and carriers, for example corn starch, gelatin, lactose, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, sodium chloride and alginic acid; and lubricants such as magnesium stearate, sodium stearate and other metallic stearates, stearic acid, glycerol stearate, silicone fluid, talc waxes, oils and colloidal silica. Flavouring agents such as peppermint, oil of wintergreen, cherry flavouring or the like can also be used. It may be desirable to add a colouring agent to make the dosage form readily identifiable. Tablets may also be coated by methods well known in the art.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active agent in a free flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may be optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active agent.

Other formulations suitable for oral administration include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active agent in an inert base such as gelatine and glycerine, or sucrose and acacia; and mouthwashes comprising the active agent in a suitable liquid carrier.

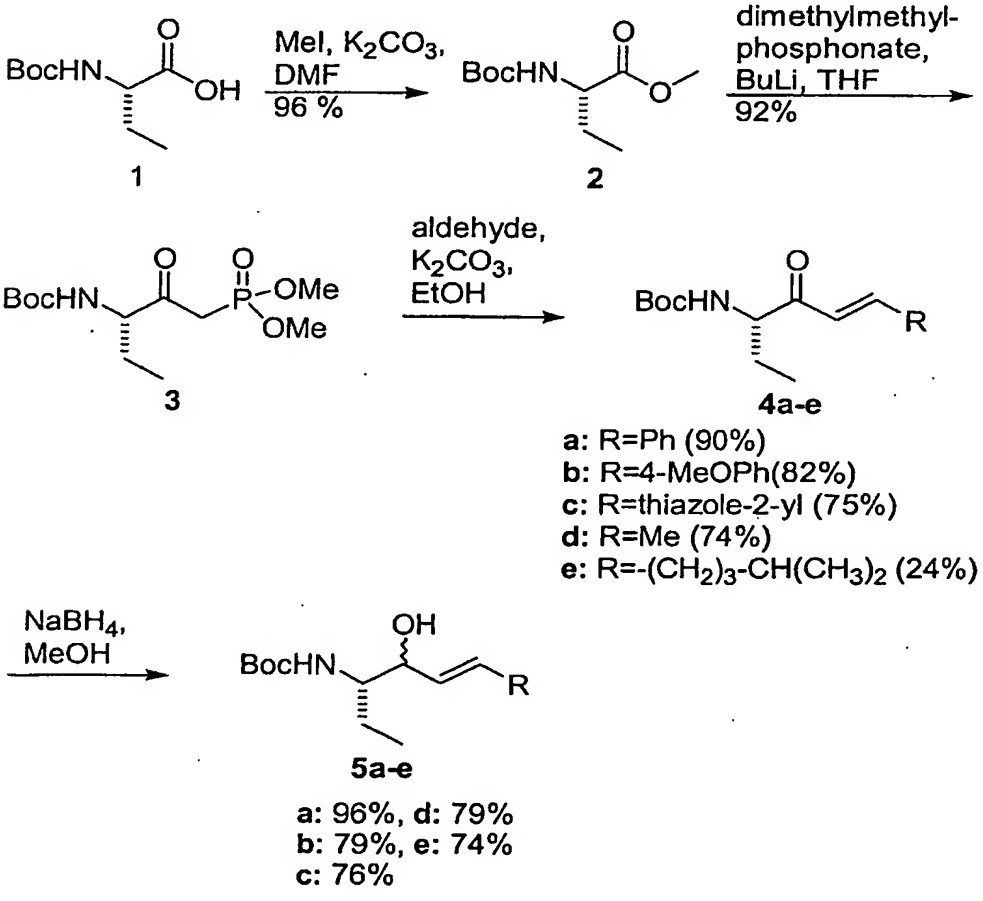
As is prudent with viral therapy, the compound of formula I/II may be co-administered with one or more further HCV antivirals/pharmaceuticals, of which ribovirin and/or interferon are the only currently available products. However various HCV polymerase inhibitors serine inhibitors and

helicase inhibitors are in the pipeline and can be expected to form the basis of efficacious combinations with the composition of the invention

In treating conditions caused by HCV, the compounds of formula I/II are preferably administered in an amount to achieve a plasma level of around 100 to 5000 nM, such as 300 to 2000 nM. This corresponds to a dosage rate, depending on the bioavailability of the formulation, of the order 0.01 to 10 mg/kg/day, preferably 0.1 to 2 mg/kg/day. A typical dosage rate for a normal adult will be around 0.05 to 5 g per day, preferably 0.1 to 2 g such as 500-750 mg, in one to four dosage units per day. As with all pharmaceuticals, dosage rates will vary with the size and metabolic condition of the patient as well as the severity of the infection and may need to be adjusted for concomitant medications.

Scheme 1 below shows a typical route to compounds of formula I.

Scheme 1 Synthesis of key intermediates **5a-e**



Compounds of the invention, for example (**10a-e**, **11a-e**, **12a-e** and **14**) were synthesised starting from Boc protected *L*-α-aminobutyric acid (Boc-Abu-OH, **1**), which was transformed to phosphonate **3**, and reacted further in a Horner-Wadsworth-Emmons reaction to give the trans-enones. The ketones moiety of the trans-enones were subsequently reduced to the corresponding alcohols, the Boc groups cleaved off and the resulting amines coupled to the pentapeptide **6** giving **10a-e** after deprotection. Oxidation of the alcohols delivered the ketones **11a-e** after deprotection. The saturated ketones **12a-e** were prepared by chemo-selective hydrogenation of the C-C double bonds followed by deprotection.

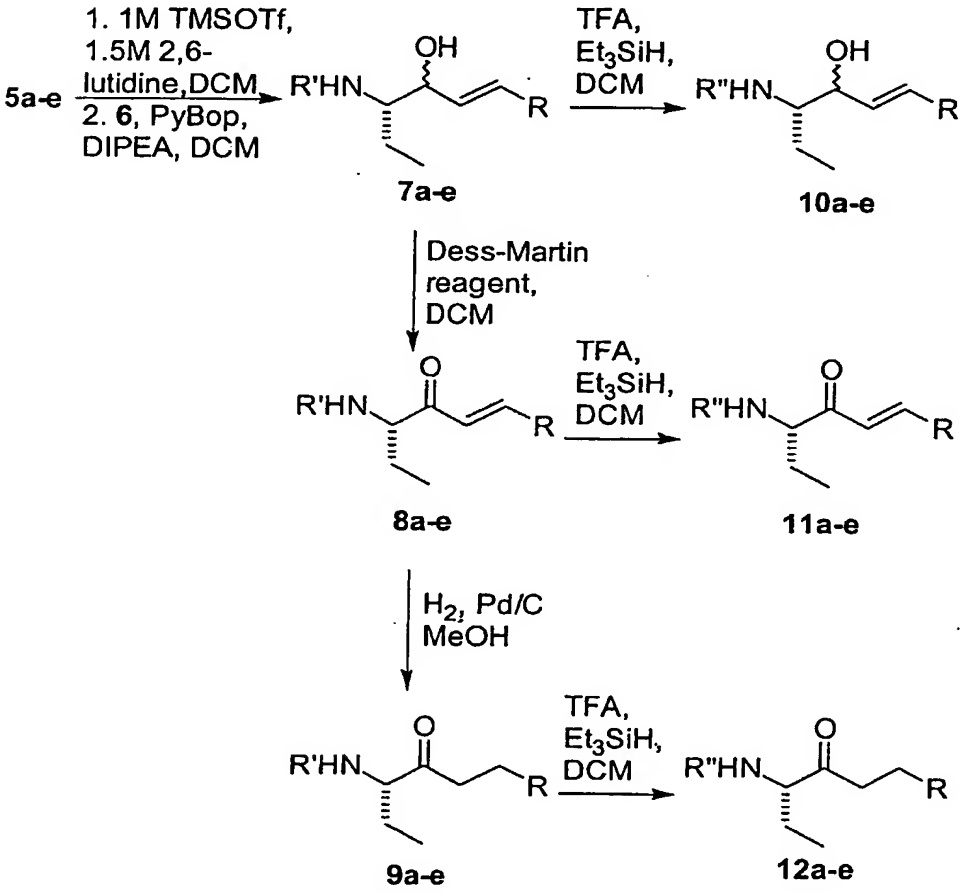
The Boc protected amino acid **1** was converted to the methyl ester **2** in 96% yield, using methyl iodide and potassium carbonate in DMF (Scheme 1) and reacted further with 6 equiv. of the lithium salt of dimethyl methylphosphonate at -78°C in THF, according to Chakravarty *et al.*,[Chakravarty, 1989 J Med Chem 32 1886-1890] to yield the phosphonate **3** in 92% yield. The trans-enones **4a-e** were obtained in good to moderate yields (24-90%) using Horner-Wadsworth-Emmons conditions, *i.e.*, by reacting the phosphonate **3** with the appropriate aldehyde in dry ethanol using 1 equiv. of potassium carbonate as base.[Benedetti, 1997 J Org Chem 62 9348-9353] Initially this reaction was accompanied by racemisation, and all attempts to suppress racemisation at the α-carbon of the trans-enones failed. Numerous different bases were explored, *e.g.* NaH in THF, [Maugras, 1990 Tetrahedron 46 2807-2816], DIPEA (*N,N*-ethyldiisopropylamine), Et_3N, DBU or diisopropylamine in CH_3CN with or without addition of LiCl/LiBr, [Blanchette, 1984 Tet Lett 25 2183-2186; Chung, 1997 Tet Asymmetry 8 3027-3030] without success. However, with potassium carbonate as a base, the racemisation of the condensation products could be minimised. 5-Methylhexanal, used in the formation of condensation product **4e**, was synthesised by oxidation of 5-methyl-1-hexanol employing pyridinium dichromate (PDC) in CH_2Cl_2.[Graham, 1994 J Org Chem59 2956-2966] Cleavage of the Boc group on compounds **4a-e** was unsuccessful and therefor the ketones were reduced using sodium borohydride to produce the alcohols **5a-e** in 74-96% yield as diastereomeric mixtures. Synthesis of the pentapeptide, Ac-Asp(O*t*Bu)-D-Glu(O*t*Bu)-Leu-Ile-Cha-OH (**6**), was performed using a Fmoc solid phase methodology on SASRIN™ [Katritzky, 1997 Tet Lett 38 7849] yielding the pure acid **6** [Sieber, 1987 Tet Lett 28 6147-6150] [Mergler, 1988 Tet Lett 29 4009-4012].

Boc deprotection was then performed by stirring **5a-e** with 1 M TMSOTf and 1,5 M 2,6-lutidine in CH_2Cl_2 to furnish the corresponding free amines (Scheme 2).[Zhang, 1998 Tet Lett 397439-7442].

Compounds of formula II are readily prepared using the corresponding methodology applied to the cyclopropyl amino acid templates disclosed in the abovementioned Boehringer Ingelheim and Bristol Myers Squibb patents.

The novel P1 replacements described herein are N terminal extended as illustrated below using formula I and model pentapeptides.

Scheme 2 Synthesis of target compounds **10-12a-e**



R' =Ac-Asp(O*t*Bu)-D-Glu(O*t*Bu)-Leu-Ile-Cha-
R"=Ac-Asp-D-Glu-Leu-Ile-Cha-

Subsequent coupling of the corresponding amines with the acid **6** was accomplished using benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP) and DIPEA in CH_2Cl_2 furnishing **7a** (66%), **7b** (87%), **7c** (50%), **7d** (52%) and **7e** (64%).[Frérot, 1991 #19]

Attempts to cleave off the Boc group using the standard conditions, *e.g.* TFA and HCl, resulted in decomposition of the alcohols **5a-e**.

Oxidation of compound **7a-e** to the ketones **8a** (69%), **8b** (53%), **8c** (73%), **8d** (78%) and **8e** (96%) was performed using Dess-Martin periodinane reagent in CH_2Cl_2 [Dess, 1983 J Org Chem 48 4155-4156].

The unsaturated ketones **8a-e** were hydrogenated over palladium on carbon in EtOAc delivering the saturated ketones **9a-e** in quantitative yields. Finally, the *t*-butyl esters were cleaved in compounds **7a-e**, **8a-e** and **9a-e**, using TFA in CH_2Cl_2 containing Et_3SiH as scavenger, to afforded the target compounds **10a-e**, **11a-e** and **12a-e** in quantitative yields.[Metha, 1992 Tet Lett 33 5441-5444]

The reference hexapeptide **14**, Ac-Asp-D-Glu-Leu-Ile-Cha-Abu-OH was synthesised by coupling of *t*-butyl *L*-α-aminobutyrate (H-Abu-O*t*Bu) with pentapeptide **6** using PyBop and DIPEA in CH_2Cl_2 yielding the protected hexapeptide Ac-Asp(O*t*Bu)-D-Glu(O*t*Bu)-Leu-Ile-Cha-Abu-O*t*Bu **13** in 52% yield. The *t*-butyl esters were then cleaved off, as above, furnishing unprotected **14** in quantitative yield.

Although Scheme 2 has been illustrated with a model recognition sequence, it will be apparent that peptide coupling to other P2-Pn sequences, such as those exemplified in the above described patents is well within the skill of those in the art.

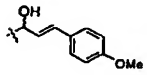
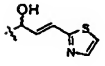
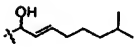
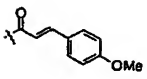
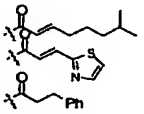
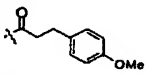
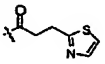
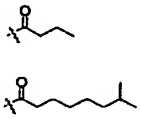
Detailed description

Inhibition assay. The inhibition of full-length hepatitis C NS3 was measured essentially as described elsewhere [Poliakov, 2002 Prot Expression & Purificaiton 25 363 371]. Briefly, the hydrolysis of a depsipeptide substrate, Ac-DED(Edans)EEAbuψ[COO]ASK(Dabcyl)-NH_2 (AnaSpec, San José, USA), was measured spectrofluorometrically in the presence of a peptide cofactor, KKGSVVIVGRIVLSGK (Åke Engström, Department of Medical Biochemistry and Microbiology, Uppsala University, Sweden).[Landro, 1997 #Biochem 36 9340-9348] The enzyme (1 nM) was incubated in 50 mM HEPES, pH 7.5, 10 mM DTT, 40% glycerol, 0.1% n-octyl-β-D-glucoside, with 25 μM cofactor and inhibitor at 30 °C for 10 min, whereupon the reaction was initiated by addition of 0.5 μM substrate. Inhibitors were dissolved in DMSO, sonicated for 30 s and vortexed. The solutions were stored at –20°C between measurements.

Table 1

Percent inhibition at 10 μM and 1 μM and inhibition constant against full length NS3 (protease-helicase/NTPase) protease; nm=not measured.

Ac-Asp-D-Glu-Leu-Ile-Cha—N(H)—R

R	Cpd	% inhib at 10 μM	% inhib at 1 μM	K_i (μM)
	**14**	60	17	1.54 ± 0.16
	**10a**	8	nm	nm
	**10b**	7	nm	nm
	**10c**	47	nm	2.30 ± 0.21
	**10d**	7	nm	nm
	**10e**	64	nm	0.98 ± 0.09
	**11a**	96	58	0.21 ± 0.03
	**11b**	100	64	0.18 ± 0.01
	11c	95	50	0.32 ± 0.03
	**11d**	96	54	0.20 ± 0.01
	**11e**	95	42	0.39 ± 0.02
	**12a**	82	25	0.98 ± 0.1
	**12b**	81	30	0.88 ± 0.05
	**12c**	64	nm	nm
	12d	80	40	0.65 ± 0.04
	12e	91	31	0.46 ± 0.07

The final concentration of DMSO in the assay sample was adjusted to 3.3%. The rate of hydrolysis was corrected for inner filter effects according to published procedures.[Liu, 1999 Analytical Biochemistry 267 331-335] K_i values were estimated by non-linear regression analysis (GraFit, Erithacus Software, Staines, MX, UK), using a model for competitive inhibition and a fixed value for K_m (0.15 μM). A minimum of two replicates was performed for all measurements.

General. All glassware was dried over an open flame before use in connection with an inert atmosphere. Concentrations were performed under reduced pressure at <40 °C (bath temperature). Thin layer chromatography was performed using silica gel 60 F-254 plates with detection by UV and charring with ninhydrine or $KMnO_4$. Silica gel (0.040-0.063 mm) was used for column chromatography. Me_4Si (0.0 ppm) was used as an internal standard in ^1H NMR and Me_4Si or $CDCl_3$ (77.0 ppm) were used in ^{13}C NMR. MALDI-TOF spectra were recorded on a Bruker Biflex III using 2',4',6'-trihydroxy-acetophenone monohydrate (THAP) as matrix. Unless stated otherwise, all materials were obtained from commercial suppliers and used without further purification. The preparative RP-HPLC was performed on a Wares-Micromass: 600 controller and ZMD mass on a Xterra MS C8 (5 μm, 19x100mm), using an acetonitrile/H_2O gradient with 10 mM NH_4HCO_3, using MS detection (positive ionisation with ES). The analytical RP-HPLC was performed on a Waters-Micromass: 2790 Waters pump, 996 DAD Waters, and Micromass ZMD mass on a Phenomex C18 Synergi Max Rp-80Å, (4 μ, 50x4.6 mm), using an acetonitrile/H_2O gradient with 10 mM NH_4HCO_3, using UV (DAD and 214 and 254 nm) and MS detection (positive ionisation with ES).

General method for the preparation of 5a-e. Oven dried K_2CO_3 (268 mg, 1.94 mmol) was added to a stirred solution of phosphonate **3** [Chakravarty, 1989 #660] (600 mg, 1.94 mmol) and the appropriate aldehyde (2 mmol) in absolute EtOH (15 mL). After 16 h the reaction mixture was filtered and the filtrate was neutralised by glacial acetic acid. The solvent was removed and the residue was portioned between EtOAc and saturated aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc and the combined organic phases were dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography (solvent system A; toluene; toluene-EtOAc 20:1, solvent system B; toluene-EtOAc 3:1) providing the ketones **4a-e**.

$NaBH_4$ (1 equiv.) was added at 0 °C in small portions over 10 min, to a stirred solution of **4a-e** (1 equiv.) in MeOH. After 2.5 h at 0 °C the solution was neutralised with glacial acetic acid, the solvent was removed and the residue was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc and the combined organic phases were dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography (solvent system C; toluene; toluene-EtOAc 6:1, solvent system D; toluene-EtOAc 1:1) providing the alcohol **4a-e** as a diastereomeric mixture.

(4S)-4-[*N*-(*tert*-Butyloxycarbonyl)amino)]-3-hydroxy-1-benzyl-1-hexen 5a. The title compound was prepared in a two step synthesis according to general procedure, *vide supra*. The intermediate **4a** was prepared in 90% yield (507 mg, 1.8 mmol) according to general procedure, *vide supra* (solvent system A). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8, 155.3, 143.8, 134.0, 130.5, 128.7, 128.2, 122.5, 79.5, 58.8, 28.3, 25.3, 9.20.

The title compound was prepared in 96% yield (289 mg, 1.0 mmol) according to general procedure, *vide supra* (solvent system C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.26 (m, 4H), 6.64, 6.16 (d, 1H), 6.26-6.16 (m, 1H), 4.82, 4.7, (d, 1H), 4.37, 4.28 (bs, 1H), 3.73-3.46 (m, 1H), 3.47 (bs, 1H), 1.72-1.31 (m, 2H), 1.40, 1.43 (s, 9H), 0.96 (t, 3H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 136.9, 131.5, 131.9, 128.8, 128.7, 128.5, 127.9, 126.8, 126.7, 80.0, 75.5, 74.5, 57.6, 57.0, 28.6, 23.6, 11.1,11.0; Anal. Calcd for ($C_{17}H_{25}NO_3$): C, 70.1; H, 8.7; N, 4.8. Found: C, 69.7; H, 8.6; N, 4.8.

(4S)-4-[*N*-(*tert*-Butyloxycarbonyl)amino)]-3-hydroxy-1-(4-methoxybenzyl)-1-hexen 5b. The title compound was prepared in a two step synthesis according to general procedure, *vide supra*. The intermediate **4b** was prepared in 82% yield (590 mg, 1.6 mmol) according to general procedure, *vide supra* (solvent system A). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 162.1, 155.7, 144.2, 130.5, 127.2, 120.7, 114.7, 79.7, 59.0, 55.6, 28.6, 25.9, 9.4.

The title compound was prepared in 79% yield (283 mg, 0.88 mmol) according to general procedure, *vide supra* (solvent system C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.28 (m, 2H), 6.86-6.81 (m, 2H), 6.55, 6.57 (d, 1H), 6.11-6.00 (m, 1H), 4.62, 4.72 (bd, 1H), 4.33, 4.24 (m, 1H), 3.8 (s, 3H), 3.76-3.53 (m, 2H), 3.13 (bd, 1H), 1.67-1.31 (m 11H). 0.96 (t, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 157.3, 131.5, 129.7, 128.0, 127.9, 126.1, 114.2, 114.2, 80.0, 75.7, 74.8, 57.3, 55.5, 28.6, 23.7, 11.1, 10.9; Anal. Calcd for ($C_{18}H_{27}NO_4$): C, 67.3; H, 8.5; N, 4.4. Found: C, 67.3; H, 8.5; N, 4.3.

(4S)-4-[*N*-(*tert*-Butyloxycarbonyl)amino)]-3-hydroxy-1-(thiazol-2-yl)-1-hexen 5c.The title compound was prepared in a two step synthesis according to general procedure, *vide supra*. The intermediate **4c** was prepared in 75% yield (500 mg, 1.7 mmol) according to general procedure, *vide supra* (solvent system B). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 163.6, 155.4, 145.3, 134.8, 126.3, 122.3, 80.0, 59.7, 28.5, 25.2, 9.5.

The title compound was prepared in 76% yield (382 mg, 1.3 mmol) according to general procedure, *vide supra* (solvent system D). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70, 7.68 (d, 1H), 7.17, 7.19 (d, 1H), 6.90 (d, 1H), 6.55 6.60 (d, 1H), 4.9, 4.8 (d, 1H), 4.38 (m, 1H). 3.8-3.4 (m,

2H), 1.68-1.33 (m, 11H), 0,94 (t, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 157.3, 143.3, 135.7, 124.4, 118.6, 80.1, 74.6, 73.0, 57.4, 56.6, 28.5, 23.6, 11.1, 11.0; Anal. Calcd for ($C_{14}H_{22}N_2O_3S$): C, 56.4; H, 7.4; N, 9.4. Found: C, 56.3; H, 7.5; N, 9.1.

(5S)-5-[*N*-(*tert*-Butyloxycarbonyl)amino)]-4-hydroxy-2-hepten 5d.The title compound was prepared in a two step synthesis according to general procedure, *vide supra*. The intermediate **4d** was prepared in 74% yield (335 mg, 1.4 mmol) according to general procedure, *vide supra* (solvent system A). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 155.6, 144.8, 128.6, 79.6, 58.3, 28.4, 25.5, 18.5, 9.2.

The title compound was prepared in 79% yield (222 mg, 0.94 mmol) according to general procedure, *vide supra* (solvent system C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (m, 1H), 5.44 (m, 1H), 4.74, 4.63 (bd, 1H), 4.06, 3.98 (m, 1H), 3.52-3.38 (m, 2H), 3.13 (bs, 1H), 1.66 (d, 3H), 1.61- 1.19 (m, 11H), 0.90(t, 3H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 129.9, 128.7, 128.5, 79.7, 75.4, 74.4, 57.3, 56.8, 28.6, 23.5, 18.0, 18.0, 10.9, 10.8; Anal. Calcd for ($C_{12}H_{23}NO_3$): C, 62.9; H, 10.11; N, 6.1. Found: C, 62.7; H, 10.1; N, 5.9.

(3S)-3-[*N*-(*tert*-Butyloxycarbonyl)amino)]-4-hydroxy-10-methyl-5-undecaen 5e. The title compound was prepared in a two step synthesis according to general procedure, *vide supra*. The intermediate **4e** was prepared in 24% yield (140 mg, 0.47 mmol) according to general procedure, *vide supra* (solvent system A). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.3, 155.7, 149.9, 127.1, 79.6, 58.4, 38.6, 33.1, 28.5, 28.0, 26.0, 25.8, 22.7, 9.3.

The title compound was prepared in 74% yield (104 mg, 0.35 mmol) according to general procedure, *vide supra* (solvent system C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.64-5.55 (m, 1H), 5.38-5.30 (m, 1H), 5.00-4.80 (m, 1H), 3.98-3.90 (m, 1H), 3.48-3.30 (m, 3H), 1.95-1.90 (m, 2H), 1.34 (s, 9H), 1.52-1.13 (m, 4H), 0.83 (t, 3H), 0.77 (s, 3H), 0.75 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 133.8, 133.5, 139.8, 128.6, 79.6, 75.0,.74.0, 57.3, 56.8, 39.0, 38.6, 32.7, 28.4, 27.9, 27.1, 23.2, 22.6, 10.8, 10.6; Anal. Calcd for ($C_{17}H_{33}NO_3$): C, 68.2; H, 11.1; N, 4.7. Found: C, 68.4; H, 11.1; N, 4.4.

Ac-Asp(O*t*Bu)-D-Glu(O*t*Bu)-Leu-Ile-Cha-OH 6. The peptide was synthesised using standard Fmoc solid-phase peptide synthesis techniques. Fmoc-Cha-OH (5 eqiuv.) was loaded to the SASRIN^{TM} (1 equiv.) using 2,6-dichlorobenzoyl chloride (5 equiv.) and pyridine (5.5 equiv.) in DMF with a loading time of 16 h. The resin was washed with MeOH, DMF, and DCM. Removal of the Fmoc group was achieved by reaction with 20% piperidine in DMF for 10 + 10 min.

Peptide elongation was performed using Fmoc-AA-OH (2 equiv.), DIC (2 equiv.) and HOBt (2 equiv.) in DCM. The peptide was cleaved from the resin using 3% TFA in DCM and Et_3SiH as scavenger, producing **6**. ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 174.4, 167.9, 172.6, 172.0, 171.9, 171.7, 171.5, 57.4, 53.0, 52.1, 49.9, 49.9, 40.0, 38.7, 36.4, 35.2, 33.7, 33.2, 31.9, 29.9, 26.0, 25.8, 25.6, 25.5, 24.3, 24.3, 22.4, 21.7, 20.6, 14.6, 10.0.

General method for the preparation of 7a-e Compound **5a-e** was added to a solution of TMSOTf (1M, 1 mL) and 2,6-lutidine (1.5M, 1 mL) in CH_2Cl_2. After 6 h of stirring the mixture was evaporated. PyBop (1 equiv.), the pentapeptide **6** (1 equiv.) and DIPEA (2 equiv.) was added to a stirred solution of the residue in CH_2Cl_2. After 16 h the reaction mixture was washed with aqueous 5% $KHSO_4$ (2x) and aqueous 5% $NaHCO_3$ (2x), dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2; CH_2Cl_2-MeOH 40:1) to give the target compound **7a-e**.

(4S)-4-[*N*-(Ac-Asp(O*t*Bu)-D-Glu(O*t*Bu)-Leu-Ile-Cha-)amino)]-3-hydroxy-1-benzyl-1-hexen 7a. The title compound was prepared in 66% yield (161 mg, 0.17 mmol) according to general procedure, *vide supra*. ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 173.4, 172.7, 172.1, 172.0, 171.9, 170.2, 136.8, 131.2, 121.2, 128.7, 128.4, 128.4, 127.4, 126.4, 81.9, 81.0, 74.7, 59.0, 56.3, 53.4, 53.1, 53.0, 51.5, 40.1, 39.9, 36.4, 36.3, 33.9, 33.5, 31.7, 31.6, 29.6, 27.8, 26.3, 26.1, 25.8, 25.0, 24.7, 22.7, 22.3, 22.0, 21.3, 15.2, 11.0, 10.5; MS (MALDI-TOF) m/z mass calcd for: $C_{52}H_{84}N_6O_{11}$, 968.62 found: 1007.58 (MK^+) 998.58 (MNa^+).

(4S)-4-[*N*-(Ac-Asp(O*t*Bu)-D-Glu(O*t*Bu)-Leu-Ile-Cha-)amino)]-3-hydroxy-1-(4-methoxybenzyl)-1-hexen 7b. The title compound was prepared in 87% yield (217 mg, 0.22 mmol) according to general procedure, *vide supra*. ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 173.5, 172.6, 172.1, 172.1, 172.0, 170.0, 169.8, 159.1, 140.9, 129.7, 127.6, 126.6, 113.7, 113.7, 74.9, 58.9, 56.2, 54.9, 54.6, 53.3, 53.0, 50.7, 42.6, 40.0, 36.3, 36.3, 33.8, 33.5, 31.5, 27.6, 26.0, 25.7, 25.0, 24.6, 22.5, 22.0,21.0, 17.9, 16.5, 15.0, 12.2, 10.8, 10.3; MS (MALDI-TOF) m/z mass calcd for: $C_{53}H_{86}N_6O_{12}$, 998.63 found: 1037.60 (MK^+) 1021.61 (MNa^+).

(4S)-4-[*N*-(Ac-Asp(O*t*Bu)-D-Glu(O*t*Bu)-Leu-Ile-Cha-)amino)]-3-hydroxy-1-(thiazol-2-yl)-1-hexen 7c. The title compound was prepared in 50% yield (164 mg, 0.17 mmol) according to general procedure, *vide supra*. ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 172.6, 172.5, 172.3, 172.2, 172.1, 172.0, 170.2, 170.1, 167.4, 142.4, 142.3, 136.7, 123.5, 118.6, 118.5, 81.9, 80.9, 73.5,

59.6, 55.9, 55.8, 55.7, 53.9, 53.8, 53.2, 51.7, 51.6, 50.7, 42.8, 36.4, 34.0, 31.6, 31.5, 27.8, 26.3, 26.3, 26.2, 26.1, 25.8, 25.2, 24.7, 22.5, 22.3, 21.3, 18.2, 16.7, 15.2, 12.4, 11.1, 11.0,10.5, 10.4; MS (MALDI-TOF) m/z mass calcd for: $C_{49}H_{81}N_7O_{11}S$, 975.57 found: 1014.45 (MK^+) 998.49 (MNa^+) 976.51 (MH^+).

(5S)-5-[*N*-(Ac-Asp(O*t*Bu)-D-Glu(O*t*Bu)-Leu-Ile-Cha-)amino)]-4-hydroxy-2-hepten 7d. The title compound was prepared in 52% yield (140 mg, 0.15 mmol) according to general procedure, *vide supra*. ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 173.6, 172.6, 172.3, 172.2, 172.2, 172.1, 170.3, 130.2, 127.8, 81.9, 80.9, 74.9, 59.4, 56.5, 54.8, 53.9, 53.4, 51.7, 50.9, 46.4, 46.3, 42.9, 40.1, 39.1, 36.5, 36.3, 34.1, 33.8, 31.8, 31.7, 28.0, 26.5, 26.4, 26.0, 25.4, 24.8, 22.8, 22.5, 22.5, 21.8, 18.4, 17.8, 16.9, 15.4, 12.6, 11.2, 11.2, 10.7; MS (MALDI-TOF) m/z mass calcd for: $C_{47}H_{82}N_6O_{11}$, 906.60 found: 945.58 (MK^+) 929.63 (MNa^+) 907.65 (MH^+).

(3S)-3-[*N*-(Ac-Asp(O*t*Bu)-D-Glu(O*t*Bu)-Leu-Ile-Cha-)amino)]-4-hydroxy-10-methyl-5-undecaen 7e. The title compound was prepared in 64% yield (200 mg, 0.20 mmol) according to general procedure, *vide supra*. ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 173.7, 172.6, 172.3, 172.1, 172.1, 170.4, 170.3, 132.7, 128.7, 82.0, 81.0, 74.9, 59.5, 56.7, 54.9, 54.0, 53.4, 53.4, 51.8, 50.9, 43.0, 40.1, 39.1, 38.7, 36.6, 36.3, 34.2, 33.8, 32.7, 31.9, 31.8, 28.0, 26.5, 25.4, 26.1, 25.4, 25.3, 24.9, 22.8, 22.6, 22.6, 21.6, 18.5, 17.0, 15.4, 12.7, 11.3, 10.8; MS (MALDI-TOF) m/z mass calcd for: $C_{52}H_{92}N_6O_{11}$, 976.68 found: 1015.64 (MK^+) 999.68 (MNa^+).

General method for the preparation of 8a-e. Dess-Martin reagent (1 equiv.) was added to a stirred solution of the alcohol **7a-e** in CH_2Cl_2 and the mixture was stirred for 16 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 and washed with $Na_2S_2O_3$ (7 equiv.) in aqueous saturated $NaHCO_3$ (2x) and water (1x). The combined aqueous phases were washed with CH_2Cl_2 (2x) and the combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2; CH_2Cl_2-MeOH 40:1) and on preparative RP-HPLC producing the target compound **8a-e.**

(4S)-4-[*N*-(Ac-Asp(O*t*Bu)-D-Glu(O*t*Bu)-Leu-Ile-Cha-)amino)]-1-benzyl-1-hexen-3-one 8a. The title compound was prepared in 69% yield (70 mg, 0.07 mmol) according to general procedure, *vide supra*. ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 172.9, 172.3, 172.2, 172.1, 171.8, 170.2, 144.8, 134.5, 131.07, 129.1, 128.8, 122.4, 81.9, 81.1, 59.6, 58.6, 58.5, 53.1, 51.5, 51.4,

50.6, 40.7, 39.4, 36.7, 34.1, 33.7, 32.5, 31.9, 28.0, 26.5, 26.3, 26.2, 26.1, 25.0, 24.9, 24.6, 22.9, 22.5, 21.5, 15.5, 11.0, 9.7; MS (MALDI-TOF) m/z mass calcd for: $C_{52}H_{82}N_6O_{11}$, 966.60 found: 1005.65 (MK^+) 989.68 (MNa^+); RP-LC MS (EI) found: 966.57 (MH^+).

(4S)-4-[*N*-(Ac-Asp(O*t*Bu)-D-Glu(O*t*Bu)-Leu-Ile-Cha-)amino)]-1-(4-methoxybenzyl)-1-hexen-3-one 8b. The title compound was prepared in 53% yield (60 mg, 0.06 mmol) according to general procedure, *vide supra*. ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.3, 173.6, 173.5, 172.9, 172.3, 172.3, 172.1, 172.0, 170.2, 162.2, 144.8, 130.7, 127.2, 120.1, 114.6, 81.8, 81.18, 58.6, 58.5, 58.4, 55.4, 53.2, 51.4, 50.7, 40.7, 39.4, 36.7, 34.1, 33.7, 32.4, 32.9, 29.7, 27.9, 26.5, 25.3, 26.2, 26.1, 25.0, 24.9, 24.7, 24.7, 22.9, 22.4, 21.4, 15.4, 11.0, 9.7; MS (MALDI-TOF) m/z mass calcd for: $C_{53}H_{84}N_6O_{12}$, 996.61 found: 1035.63 (MK^+) 1019.54 (MNa^+) RP-LC MS (EI) found: 997.64 (MH^+).

(4S)-4-[*N*-(Ac-Asp(O*t*Bu)-D-Glu(O*t*Bu)-Leu-Ile-Cha-)amino)]-1-(thiazole-2-yl)-1-hexen-3-one 8c. The title compound was prepared in 73% yield (70 mg, 0.0.7 mmol) according to general procedure, *vide supra*. ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5, 173.7, 173.3, 172.9, 172.3, 172.2, 172.1, 172.0, 170.2, 144.7, 134.6, 126.7, 122.6, 81.8.81.0, 59.3, 59.2, 58.6, 53.1, 51.4, 50.7, 40.6, 39.4, 36.7, 34.1, 33.7, 32.6, 31.8, 31.7, 29.7, 27.9, 26.5, 26.3, 26.1, 26.1, 25.0, 24.9, 24.0, 22.9, 22.3, 21.3, 15.4, 10.9, 9.7; MS (MALDI-TOF) m/z mass calcd for: $C_{49}H_{79}N_7O_{11}S$, 973.56 found: 1012.50 (MK^+) 996.54 (MNa^+) 974.57 (MH^+); RP-LC MS (EI) found: 974.59 (MH^+).

(5S)-5-[*N*-(Ac-Asp(O*t*Bu)-D-Glu(O*t*Bu)-Leu-Ile-Cha-)amino)]-2-hepten-4-one 8d. The title compound was prepared in 78% yield (78 mg, 0.09 mmol) according to general procedure, *vide supra*. ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 198.0, 173.4, 172.9, 172.8, 172.3, 172.2, 172.0, 171.8, 145.5, 128.3, 81.8, 81.1, 58.9, 58.3, 58.1, 57.8, 53.3, 53.2, 53.1, 53.0, 52.7, 52.3, 50.6, 50.3, 40.1, 39.0, 36.8,36.7, 35.9, 34.2, 34.1, 33.9, 33.7, 32.5, 31.8, 31.7, 29.8, 28.0, 26.5, 26.3, 26.1, 26.0, 25.2, 25.0, 24.9, 24.6, 24.3, 23.0, 22.9, 22.4, 21.4, 21.2, 18.4, 18.4, 16.9, 15.4, 15.3, 13.6, 10.9, 10.8, 10.0, 9.5; MS (MALDI-TOF) m/z mass calcd for: $C_{47}H_{80}N_6O_{11}$, 904.59 found: 943.65 (MK^+) 927.66 (MNa^+) 905.67 (MH^+); RP-LC MS (EI) found: 905.60 (MH^+).

(3S)-3-[*N*-(Ac-Asp(O*t*Bu)-D-Glu(O*t*Bu)-Leu-Ile-Cha-)amino)]-10-methyl-5-undecaen-4-one 8e. The title compound was prepared in 96% yield (95 mg, 0.10 mmol) according to general procedure, *vide supra*. ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 173.4, 172.9, 172.7, 172.3, 172.2,

172.0, 171.8, 170.2, 150.4, 126.6, 81.8, 81.0, 58.3, 57.8, 53.1, 52.9, 51.3, 50.6, 40.7, 39.6, 39.4, 38.9, 38.6, 36.8, 36.7, 34.1, 33.7, 33.1, 32.5, 31.8, 28.9, 26.5, 26.3, 26.2, 26.1, 25.9, 24.9, 24.7, 22.9, 22.5, 22.4, 22.4, 22.4, 21.4, 15.4, 10.9, 9,5; MS (MALDI-TOF) m/z mass calcd for: $C_{52}H_{90}N_6O_{11}$, 974.67 found: 1015.64 (MK^+) 999.68 (MNa^+); RP-LC MS (EI) found: 975.70 (MH^+).

General method for the preparation of 9a-e. A catalytic amount of Pd/C (10%) was added to **8a-e** in MeOH. Hydrogen was added at atmospheric pressure to the system and the reaction mixture was stirred for 1 h. The suspension was then filtrated through Celite and the solvent was removed to give **9a-e**.

(4S)-4-[*N*-(Ac-Asp(O*t*Bu)-D-Glu(O*t*Bu)-Leu-Ile-Cha-)amino)]-1-benzyl-3-hexenone 9a. The title compound was prepared in 100% yield (33 mg, 0.034 mmol) according to general procedure, *vide supra*. ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.2, 173.9, 173.5, 172.8, 172.4, 172.4, 172.3, 172.2, 170.2, 141.0, 128.4, 128.4, 126.1, 81.9, 81.0, 60.3, 58.7, 53.3, 53.2, 51.3, 50.9, 40.8, 40.4, 39.1, 36.6, 36.6, 34.1, 33.7, 32.2, 31.7, 29.4, 27.8, 26.4, 26.3, 26.1, 25.9, 25.1, 24.9, 23.6, 22.7, 22.1, 21.2, 15.3, 10.9, 9.8; MS (MALDI-TOF) m/z mass calcd for: $C_{52}H_{84}N_6O_{11}$, 968.62 found: 1007.58 (MK^+) 998.58 (MNa^+).

(4S)-4-[*N*-(Ac-Asp(O*t*Bu)-D-Glu(O*t*Bu)-Leu-Ile-Cha-)amino)]-1-(4-methoxybenzyl)-3-hexenone 9b. The title compound was prepared in 100% yield (36 mg, 0.036 mmol) according to general procedure, *vide supra*. ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.3, 1173.8, 173.4, 172.8, 172.4, 172.4, 172.3, 172.2, 170.2, 158.1, 133.2, 129.4, 113.9, 81.7, 80.9, 60.3, 58.7, 55.0, 53.3, 53.2, 51.3, 50.9, 41.0, 40.4, 39.1, 36.6, 36.5, 34.1, 33.7, 32.3, 31.7, 28.5, 27.8, 26.4, 26.3, 26.1, 25.9, 25.1, 24.9, 23.6, 22.7, 22.1, 21.2, 15.3, 10.8, 9.8; MS (MALDI-TOF) m/z mass calcd for: $C_{53}H_{86}N_6O_{12}$, 998.63 found: 1037.65 (MK^+) 1021.68 (MNa^+).

4S)-4-[*N*-(Ac-Asp(O*t*Bu)-D-Glu(O*t*Bu)-Leu-Ile-Cha-)amino)]-1-(thiazole-2-yl)-3-hexenone 9c. The title compound was prepared in 100% yield (23 mg, 0.024 mmol) according to general procedure, *vide supra*. ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.9, 173.9, 173.6, 172.8, 172.4, 172.4, 172.4, 172.3, 170.2, 141.6, 119.0, 81.7, 80.9, 60.3, 58.3, 53.3, 53.2, 51.3, 50.9, 40.3, 39.1, 38.5, 36.6, 36.5, 34.1, 33.7, 32.1, 31.7, 27.8, 26.6, 26.4, 26.3, 26.1, 25.9, 25.2, 24.9, 23.6, 22.7, 22.1, 21.16, 15.3, 10.8, 9.8; MS (MALDI-TOF) m/z mass calcd for: $C_{49}H_{81}N_7O_{11}S$, 975.57 found: 1014.62 (MK^+) 998.67 (MNa^+) 976.67 (MH^+).

(5S)-5-[*N*-(Ac-Asp(O*t*Bu)-D-Glu(O*t*Bu)-Leu-Ile-Cha-)amino)]-4-heptenone 9d. The title compound was prepared in 100% yield (25 mg, 0.0.28 mmol) according to general procedure, *vide supra*. ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.4, 210.2, 173.9, 173.8, 173.2, 172.9, 172.8, 172.7, 172.4, 172.1, 172.0, 1720, 170.2, 170.1, 81.9, 81.7, 81.1, 60.2, 60.1, 59.1, 58.7, 53.4, 53.3, 53.2, 51.3, 51.2, 50.8, 41.4, 41.2, 40.6, 40.4, 39.1, 39.0, 36.8, 36.7, 36.6, 35.7, 34.2, 34.2, 33.9, 33.7, 32.2, 31.8, 27.9, 26.5, 26.4, 26.2, 26.1, 25.9, 25.3, 25.1, 25.9, 23.8, 23.6, 23.0, 22.8, 22.3,.21.3, 21.1, 16.9, 16.9, 15.4, 15.3, 13.5, 11.0, 10.2, 9.9; MS (MALDI-TOF) m/z mass calcd for: $C_{47}H_{82}N_6O_{11}$, 906.60 found: 945.65 (MK^+) 929.69 (MNa^+).

(3S)-3-[*N*-(Ac-Asp(O*t*Bu)-D-Glu(O*t*Bu)-Leu-Ile-Cha-)amino)]-10-methyl-4-undecaenone 9e. The title compound was prepared in 100% yield (24 mg, 0.025 mmol) according to general procedure, *vide supra*. ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.3, 173.8, 173.3, 172.9, 172.4, 172.2, 170.2, 81.8, 81.0, 60.1, 58.7, 53.3, 53.2, 51.3, 50.8, 40.4, 39.3, 39.2, 38.9, 336.7, 36.6, 34.1, 33.8, 32.2, 31.8, 29.5, 28.0, 27.9, 27.3, 26.5, 26.4, 26.1, 25.9, 25.1, 25.9, 23.8, 23.5, 22.9, 22.8, 22.4, 22.2, 21.3, 15.3, 10.9, 9.9; MS (MALDI-TOF) m/z mass calcd for: $C_{52}H_{92}N_6O_{11}$, 976.66 found: 1015.70 (MK^+) 999.72 (MNa^+).

General method for the preparation of 10a-e, 11a-e and 12a-e. Compound **7a-e**, **8a-e** or **9a-e** was added to a stirred solution of TFA (30 equiv.) and Et_3SiH (6 equiv.) in CH_2Cl_2 (100 equiv.). After 1 h toluene (3 mL) was added and the mixture was concentrated to give the free acid **10a-e**, **11a-e** and **12a-e**. The peptides were analysed by MALDI-TOF and by analytical RP-HPLC. All the measured weight were within +0.13 to +0.19 mass unit of the calculated weight ($M+H^+$, $M+Na^+$, $M+K^+$), of the compounds.

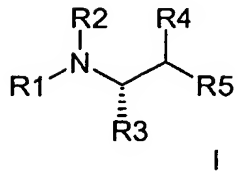
Ac-Asp-D-Glu-Leu-Ile-Cha-Abu-OH 14. H-N-Abu-OtBu * HCl (23 mg, 0.14 mmol) was added to a mixture of PyBop (65 mg, 0.13 mmol), **6** (100 mg, 0.13 mmol.) and DIPEA (47 µL, 0.27 mmol) in CH_2Cl_2. After 16 h stirring at room temperature the reaction mixture was washed with aqueous 5% $KHSO_4$ (2x) and aqueous 5% $NaHCO_3$ (2x), dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2; CH_2Cl_2-MeOH 40:1) to give Ac-Asp(O*t*Bu)-D-Glu(O*t*Bu)-Leu-Ile-Cha-Abu-O*t*Bu **13** in 52% yield (68 mg, 0.08 mmol). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 172.9, 172.4, 172.3, 171.9, 171.6, 171.5, 170.9, 169.7, 81.4, 81.2, 80.5, 57.8, 54.0, 52.6, 52.4, 50.6, 50.3, 40.1, 38.9, 36.2, 33.7, 33.6,

33.3, 31.9, 31.2, 27.3, 27.2, 26.0, 25.8, 25.7, 25.6, 24.6, 24.4, 24.4, 22.3, 21.7, 20.7, 14.8, 10.2, 9.1.

Compound **13** (25 mg, 0.03 mmol) was added to a stirred solution of TFA (85 ??????μL, 1.14 mmol) and Et_3SiH (29 μL, 0.18 mmol) in CH_2Cl_2 (185 μL, 2.9 mmol). After 1 h toluene (3 mL) was added and the solvent was removed to give the target compound **14** in quantitative yield (23 mg, 0.03 mmol). The peptide was analysed by MALDI-TOF m/z mass calcd for: $C_{36}H_{60}N_6O_{12}$, 768.43 found: 807.43 (MK^+) 791.46 (MNa^+) 769.46 (MH^+) and by analytical RP-HPLC: 791.45 (MNa^+) 769.48 (MH^+).

Claims

1. A compound of the formula I:



I

where

R^1 is a peptidic or peptidomimetic recognition sequence P2-Pn targeting the S2- Sn pockets of HCV NS-3 serine protease, where n is 3-6, which recognition sequence is peptide bonded to formula I

R^2 is H, C_1-C_3 alkyl;

R^3 is halo, amino, C_1-C_3 alkyl, optionally substituted with 1-3 halo atoms, amino or –SH.

R^4 is =O, halo, amino, –OH

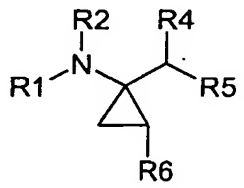
R^5 is C_1-C_6 alkyl, C_0-C_3-alkylaryl, C_0-C_3alkylhet, C_0-C_3alkylcycloC$_3$-C_6alkyl, any of which can be optionally substituted with hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkanoyl, amino, halo, carboxy, cyano, azido, mercapto, nitro, C_0-C_3-alkylaryl, C_0-C_3alkylhet, C_0-C_3alkylcycloalkyl;

with the proviso that if R_4 is =O, then the alkyl moiety of R_5 as alkylaryl or alkylhet is C_1-C_3 alkanyl or C_2-C_3 alkenyl

and pharmaceutically acceptable salts thereof

2. A compound according to claim 2, wherein R3 is n-ethyl, n-propyl, 2,2-difluoroethyl, or mercaptomethyl.

3. A compound of the formula II:



II

where

R^1 is a peptidic or peptidomimetic recognition sequence targeting the S2- Sn pockets of HCV NS-3 serine protease, where n is 3-6, which recognition sequence is peptide bonded to formula II;

R^2 is H, C_1-C_3 alkyl;

R^3 is C_1-C_3 alkyl, optionally substituted with 1-3 halo atoms or –SH;

R^4 is =O, halo, amino or –OH;

R^5 is C_1-C_8 alkyl, C_0-C_3-alkylaryl, C_0-C_3alkylheteroaryl, C_0-C_3alkylcycloC_3-C_6alkyl, any of which can be optionally substituted with hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkoxy C_1-C_6 alkyl, C_1-C_6 alkanoyl, amino, halo, cyano, azido, mercapto,-nitro, C_0-C_3-alkylaryl, C_0-C_3alkylhet, C_0-C_3alkylcycloalkyl;

R^6 is H, C_1-C_3 alkyl or wherein R6 cyclises with the (nominal) N-terminal to define a macrocycle;

with the proviso that if R_4 is =O, then the alkyl moiety of R_5 as alkylaryl or alkylhet is C_1-C_3 alkanyl or C_2-C_3 alkenyl;

and pharmaceutically acceptable salts thereof.

4. A compound according to claim 3, wherein R^6 is H.

5. A compound according to claim 3, wherein R^6 is -$CHCH_2$.

6. A compound according to claim 1 or 3, wherein R^5 is straight or branched C_3-C_8 alkyl.

7. A compound according to claim 6, containing a single unsaturated bond.

8. A compound according to claim 1 or 3 wherein R^5 is alkylaryl or alkylhet.

9. A compound according to claim 8, wherein the alkyl moiety of R^5 is C_1–C_3 alkanyl or C_2-C_3 alkenyl.

10. A compound according to claim 8, wherein the aryl moiety of R^5 is optionally substituted phenyl.

11. A compound according to claim 1 or 3, wherein R^2 is H.

12. A compound according to claim 1 or 3, wherein R^4 is -OH.

13. A compound according to claim 1 or 3, wherein R^4 is $-NH_2$ or fluoro or chloro.

14. A compound according to claim 1 or 3 wherein P2 of R^1 is the amino acid proline or 4-hydroxyproline, which hydroxy function is optionally etherified or esterified to a phenyl, benzyl, naphthyl or quinolyl group.

15. A compound according to claim 14 wherein the ether is 7-methoxy-2-phenyl-quinolin-4-yl oxy, or the ester is quinolin-1-oyl.

16. A compound according to claim 1 or 3, wherein P3 is an aliphatic amino acid selected from L-valyl, L-leucyl, L-isoleucyl or L- t-leucyl.

17. A compound according to claim 1, 3 or 16, wherein P4 is an aliphatic amino acid selected from L-valyl, L-leucyl, L-isoleucyl , L-t-leucyl or L-cyclohexylalanine.

18. A compound according to any of claim 1, 3 or 17, wherein P5 is the amino acid D-Glu, gamma-carboxy-D-Glu or D-Val.

19. A compound according to any of claims 1, 3 or 18, wherein P6 is the amino acid L-Asp.

20. A compound according to claim 17, 18 or 19 wherein the N-terminal of said amino acid is capped with a pharmaceutically acceptable capping group.

21. A compound according to claim 17, wherein the capping group is acetyl t-butyloxycarbonyl, benzyloxycarbonyl, pyridylcarbonyl or pyrimidylcarbonyl.